V B. Myocardium

Exposure to carbon monoxide resulting in carboxyhemoglobin levels of 10 % saturation does not influence cardiac output in subjects after a few hours (Brody and Coburn, 1969, 1970) or after 8 days (Klausen et al., , 1968). With levels exceeding 15 % saturation, there is either an increase or a decrease in cardiac output (Diamant-Berger et al., 1970; Katzschmann, 1970).

The response of the heart to muscular exercise has been assessed during exposure to carbon monoxide. Guillern et al. (1907) exposed 12 subjects to a concentration of 50 to 100 ppm and noted an increase of cardiac acceleration during effort. . Chevalier et al. (1963) previously reported a lower heart rate for exercising subjects exposed to carbon monoxide, but the concentration was not stated. Pirnay et al. (1971 a and b) reported cardiac acceleration due to muscular exercise during exposure, with carboxyhemoglobin saturation of 15 %, but no comparison was made with exercising subjects not submitting to carbon monoxide inhalation. Vogel and Gleser (1972) and Vogel et al. (1972) investigated blood levels as high as 20 % saturation and failed to show a difference in cardiac output response, although there was an exaggerated tachycardia during exercise as compared with subjects not experiencing hypoxia. The pumping capacity of the heart is not influenced by carboxyhemoglobin blood levels of up to 20 %. The changes in heart function associated with cigarette smoking discussed by Roskamm (1964) and Anderson (1971) relate to constituents of cigarette smoke other than carbon monoxide.

Exposure to carbon monoxide causes an enlargement of the heart, seen in patients who have recovered from poisoning (Jagic and Zimmerman, 1934; Kroetz, 1936; Ziegler, 1936; Flaxman, 1939; Kaliaeva, 1951). The disturbance in myocardial function is also manifested by abnormalities in the ballistocardiogram

(Gorski, 1962), reduced response of left ventricle to the nitroglycerin test (Gokina, 1971), and elevation of serum enzymes which reflect myocardial injury (Jaffe, 1965). The postmortem examination of the heart in patients dying from carbon monoxide poisoning reveals necrosis and hemorrhagic infarction, fibrosis and fatty degeneration (Koelsch, 1936; Nagel, 1937; Monaui, 1940; Breu, 1942; Binet and Betourné, 1951; Holm, 1950; Caccuri, 1955; Ritter, 1956; Klavis and Schulz, 1966; Borst, 1967; Sobotka and Sobotka, 1969; Caroff et al, 1970.

The rat has been the laboratory animal most extensively used to investigate myocardial effects of carbon monoxide. Asmussen and Paulsen (1953) exposed immature rats for 60 days to an atmosphere containing carbon monoxide. The blood levels were kept at 50 to 60% carboxyhemoglobin. Compared with control rats, the carbon-monoxide-treated rats were inferior in their ability to swim till exhausted and to withstand low oxygen tension. The carbon-monoxide-treated rats showed cardiac hypertrophy and a slight but significant increase in the relative number of coronary capillaries. Suzuki (1969) administered 1% carbon monoxide for 10 min to mature rats and the animals were sacrificed from 10 min to 24 hours after cessation of inhalation. The electron microscopic examination of the heart revealed intracellular edema, swelling of mitochondria and sarcoplasmic reticula, disruption and reduction of cristae, disappearance of mitochondria, appearance of lipofuscin pigment granules and lysosomes and increase of glycogen granules and fat droplets. The author concluded that the effects of carbon monoxide on the heart result not only from hypoxemia but also from the direct toxic effects on the specific respiratory enzymes.

Holczabek (1971) arrived at a similar conclusion following exposure of rats to 3% carbon monoxide. Slater (1950) demonstrated inhibition of dihydrocozymase oxidase of heart muscle exposed to carnon monoxide in vitro.

The direct effects of carbon monoxide on the monkey heart have not been investigated. Since there is a species difference relating to pulmonary effects, it is reasonable to suspect that this may also apply to the heart. The rabbit heart shows cardiac necrosis, which could be interpreted to be the result of hypoxemia rather than the direct effect of carbon monoxide (Veith, 1940)..

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V C. Coronary Circulation

In recent years there has been an increasing number of publications associating coronary heart disease with the carbon monoxide contained in cigarette smoke (Jaffe, 1968; Dinman, 1969; Robin et al., 1969; Goldsmith, 1970; Szöllösi et al., 1970; Tibblin, 1971; Schievelbein and Eberhardt, 1972; and Bersay Marland, 1972). The evidence for stating that the carbon monoxide content of cigarette smoke caused coronary heart disease is indirect. A review of the investigations concerned reveals that the levels of carboxyhemoglobin in the blood of habitual smokers do not cause coronary heart disease.

The effect of exposure to lower concentrations of carbon monoxide in high-pollution areas of Los Angeles has been examined by Cohen et al. (1969). The case fatality rates for patients admitted with myocardial infarction to 35 hospitals during 1958 were examined. The results indicate that there was an increase in fatality rate in high-pollution areas and that this difference was evident during periods of relatively increased carbon monoxide pollution. However, it was not possible to prove cause and effect relationship between carbon monoxide and high fatality rate, since there are other pollutants involved. In the same city, Haywood et al. (1972) examined 34 patients with acute myocardial infarction and 35 control patients with diverse diseases. Carboxyhemoglobin levels averaged 5.14% for the infarct patients and 4.8% for the controls; there was no clear-cut relationship between carbon monoxide levels and acute infarction. For patients with angina pectoris, exposure to the heavy morning freeway traffic in Los Angeles

caused a decrease in exercise performance that initiated the onset of angina (Aronow et al., 1972). The mean blood levels of carboxyhemoglobin in % were 1.12 ± 1.20 before, 5.08 ± 1.19 immediately after leaving the freeway, and 2.91 ± 0.93 two hours later. Any one of the pollutants other than carbon monoxide may be responsible for quicker development of angina after less cardiac work. Ten patients with angina pectoris were examined by Aronow and Rokaw (1971) and Aronow et al. (1971) following the smoking of low-nicotine cigarettes. After each subject had smoked 8 cigarettes, at the rate of one every 30 min, the carboxyhemoglobin level in the blood rose from 1.58 to 7.79%. This was accompanied by a decrease in exercise tolerance. These results cannot be interpreted to mean that carbon monoxide alone is the cause of the decrease in exercise tolerance. The only direct proof would be to repeat similar observations on patients inhaling carbon monoxide mixture. De Bias et al. (1972) exposed dogs with myocardial infarction to 100 ppm carbon monoxide for 14 weeks. The elevation of the blood carboxyhemoglobin level to 14% did not influence the electrocardiogram nor the serum enzymes that would be expected to accompany increasing severity of hypoxia. Carbon monoxide alone, producing up to 14% saturation of carboxyhemoglobin, does not appear to exaggerate myocardial infarction in dogs.

Exposure of rabbits for up to 14 months, resulting in a blood level of 15 to 40% carboxyhemoglobin, causes myocardial damage (Andersson, 1972). The lesions are similar to those reported for patients who have recovered from acute carbon monoxide poisoning. Some of these patients manifested anginal

attacks (Kroetz, 1936a; Beck and Suter, 1938; Hubert, 1943; Zeh, 1960) and myocardial infarction (Kroetz, 1936b; Wiktor, 1954: Anderson et al., 1967).

The effects of inhalation of 0.1 or 5% carbon monoxide, sufficient to raise the carboxyhemoglobin level to between 5 and 25% in dogs and humans, were reported by Ayres et al. (1969, 1970). There was an increase in coronary blood flow and alteration of lactate and pyruvate metabolism. Most of these changes could be accounted for by hypoxemia, although a direct effect of carbon monoxide on the coronary vessels has not been excluded.

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V D. Systemic Circulation

Cigarette smoking causes vasoconstriction of most vascular beds. These effects are brought about by nicotine contained in the smoke. The carbon monoxide absorbed during smoking does not contribute to the vascular effects. In animals, the pattern of action of carbon monoxide is vasodilatation with elevation of body temperature (Binet and Burstein, 1948; Coret and Hughes, 1964; Nielsen, 1971).

Acute carbon monoxide poisoning is accompanied by a fall in aortic blood pressure (Litzner, 1936; Deviatka, 1956; Navratil, 1956; Vyskocil and Novotny, 1956; Chudzikiewicz, 1957; Mihai and Weber, 1964; Heidrich et al., 1970). Hypotension has also been noted following exposure to carbon monoxide in dogs (Brewer, 1937; von Oettingen et al., 1941), cats (Kayser, 1939; Maurer, 1941), rabbits (Nishigori, 1932; Süpfle, 1934) and rats (Truhaut et al., 1968). The fall in blood pressure is entirely due to vasodilatation, which has been demonstrated in dogs (Sulotto et al., 1969 a and b). In man vasoconstriction of the hand reflexly induced by cold is reduced by levels of 19 and 25 % carboxyhemoglobin (Heistad and Wheeler, 1972).

The influence of carbon monoxide on capillary permeability has been investigated in humans and animals. In man, exposure to carbon monoxide for 8 days caused an increase in the permeability of the capillaries to albumin (Siggaard-Andersen et al., 1968, 1969). The increase in permeability could not be demonstrated in the calf muscle (Petersen et al., 1968). In rabbits, guinea pigs and rats there is an increase in permeability in the peritoneal cavity (Güthert et al., 1970) and subcutaneous tissue (Van Liew, 1968 a and b, 1970).

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V E. Arteries

Although no specific case of arterial disease caused by carbon monoxide associated with cigarette smoking has been reported, there have been repeated suggestions of cause and effect relationship. The facts are as follows:

1. Patients who have been exposed to acute carbon monoxide poisoning develop skeletal muscle necrosis (Mautner, 1955), Volkmann's contracture Ortizaga, 1967) or venous thrombosis (Heidrich and Klems, 1969). Similar lesions have not been reported following exposure to low levels of carbon monoxide.

2. In patients with thromboangiitis obliterans or Buerger's disease, Astrup (1964) pointed out a connection between smoking and increased affinity of hemoglobin. Astrup (1966 a and b) and Astrup et al. (1966) showed the increase in affinity for oxygen to be associated with carbon monoxide present in tobacco smoke, since higher carboxyhemoglobin levels were observed in smokers with thromboangiitis obliterans than in healthy smokers. Mulhausen et al. (1967) confirmed this observation in another group of patients. Kjeldsen and Mozes (1969) and Kjeldsen (1969) noted in a third group of patients that the carboxyhemoglobin saturations and cholesterol levels are higher in controls. Birnstingl et al. (1966) demonstrated that patients with thromboangiitis obliterans did not show a greater alteration in oxygen affinity produced by smoking than did compared with normal smokers. The possibility that carboxyhemoglobin increases blood viscosity and therefore reduces the velocity of blood circulation and hastens the tendency to thrombus formation has been excluded by measurements performed by Sølvsteen and Kristjansen (1968).

3. That exposure to carbon monoxide could lead to arteriosclerosis was proposed by Hueper (1944) as part of his anoxemia theory. Astrup and his collaborators have attempted to find experimental support for this theory in cholesterol-fed rabbits – see reviews by Astrup (1967, 1969, 1970, 1972) and by Astrup and Kjeldsen (1970). The exposure to carbon monoxide enhanced the development of atheromatosis (Astrup et al., 1970 a and b). The appearance of lesions was accompanied by elevation of serum lipid levels (Truhaut et al., 1968; Kjeldsen, 1970a), change in lactate dehydrogenase isoenzymes of the aortic arch (Hellung-Larsen et al., 1968), increased endothelial permeability (Wanstrup et al., 1969), and ultrastructural intimal changes (Kjeldsen et al., 1972). In human subjects exposed to carbon monoxide, an increase in capillary filtration rate (Siggaard-Andersen et al., 1967) and elevation of serum lipid levels (Kjeldsen and Damgaard, 1965, 1968; Kjeldsen, 1970b) have been demonstrated. It has been suggested that carbon monoxide inhibits synthesis of cholesterol, leading to accumulation of lanosterol (Gibbons and Mitropoulus, 1972). Another effect of carbon monoxide is an increase in mitochondrial enzymic activity, which stimulates lipid synthesis within the artery (Whereat, 1970). It has not been possible to develop atherosclerosis in animals exposed to carbon monoxide without supplemental cholesterol feeding.

4. Examination of individuals who have been exposed to an environment of up to 1,000 ppm carbon monoxide with carboxyhemoglobin levels of blood between 2 and 26 % for an average duration of 10.5 years did not reveal any early development of arteriosclerosis (Prerovská and Drdková, 1967 a and b;

1971). The average values of serum lipid levels did not exceed the normal range. The results of experiments on rabbits do not apply to epidemiologic surveys in humans.

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